intra-articular injection of monoiodoacetate (MIA), and the joint degeneration was assessed with the OARSI cartilage degeneration score in histological assessments of the joints of the rats.
Results: The MCP-1 itself enhanced the autocrine of MCP-1 in OA and normal human cartilage and the Expression of collagen I, V, IX, XI and Matrix metalloproteinases (MMP) increased after Stimulation of MCP-1. The MCP-1 also induced the apoptosis of normal and OA chondrocytes. The CCR-2 antagonist retarded the establishment of a monoiodoacetate (MIA)-induced animal model of OA in rats.
Conclusions: The results of this study prove that the MCP-1-CCR2 ligand-receptor axis plays an important role in the progress of the OA's pathology. Inhibition of the MCP-1-CCR2 ligand-receptor axis may retard the pathological progress of human OA. And, we speculate that lots of OA patients that etiology is unclear can gain some cues from the MCP-1-CCR2 ligand-receptor axis, according to our present study.

506
BONE GEOMETRY OF THE HIP IS ASSOCIATED WITH OBESITY AND EARLY STRUCTURAL DAMAGE – A 3.0T MRI STUDY OF COMMUNITY-BASED ADULTS

A. Teichtahl †, Y. Wang ‡, S. Smith ‡, A. Wluka ‡, M. Zhu ‡, D. Urquhart ‡, G. Giles §, R. O'Sullivan ‡, F. Cicuttini ‡. † *Baker IDI/Monash Univ., Melbourne, Australia;* ‡ *Monash Univ., Melbourne, Australia;* § *Cancer Council Victoria, Melbourne, Australia*

Purpose: The mechanism by which obesity increases the risk of hip osteoarthritis (OA) is unclear. One mechanism may be by mediating abnormalities in bony geometry, which may in turn be associated with early structural abnormalities, such as cartilage defects and bone marrow lesions (BMLs).
Methods: 141 older adults with no diagnosed hip OA had weight and body mass index (BMI) measured between 1990 and 1994 and again in 2009-10. Acetabular depth and lateral centre edge angle (LCEA), both measures of acetabular over-coverage, as well as femoral head cartilage volume, cartilage defects and BMLs were assessed with 3.0T MRI performed in 2009-10.
Results: Current BMI, weight and weight gain were associated with increased acetabular depth and LCEA (all $p \leq 0.01$). For every one millimetre increase in acetabular depth, femoral head cartilage volume reduced by $59mm^3$ (95% CI $98mm^3$ to $20mm^3$, $p < 0.01$). Greater acetabular depth was associated with an increased risk of cartilage defects (OR 1.22, 95% CI 1.03–1.44, $p = 0.02$) and BMLs (OR 1.29, 95% CI 1.01–1.64, $p = 0.04$) in the central region of the femoral head. LCEA was not associated with hip structure.
Conclusions: Obesity is associated with acetabular over-coverage. Increased acetabular depth, but not the LCEA, is associated with reduced femoral head cartilage volume and an increased risk of cartilage defects and BMLs. Minimising any deepening of the acetabulum, for example through weight management, might help to reduce the incidence of hip OA.

507
THE BENEFICIAL ROLE OF PAI-1 IN BONE-CARTILAGE INTERACTION

M.F. Pustjens †, S.C. Mastbergen †, W.H. Noort-Van der Laan ‡†, R.J. Van Heerwaarden ‡, F.P. Lafeber †. † *Univ. Med. Ctr. Utrecht, Utrecht, Netherlands;* ‡ *St. Maartenskliniek, Woerden, Netherlands*

Purpose: In osteoarthritis (OA) subchondral bone changes are seen in addition to cartilage changes. In treatments targeted at bone, such as treatment with strontium ranelate (Reginster, 2013), or treatments with bone involvement such as osteotomy (Jung et al, 2014) or joint distraction (Intema et al, 2012) cartilage repair has been demonstrated. These studies support the hypothesis that a reset of bone can lead to cartilage repair. However, the exact biochemical interactions and how this contributes to repair and degradation processes is less well known. Plasminogen activator inhibitor (PAI)-1, inhibits plasmin which accounts for higher levels of MMPs in OA. It is expressed in subchondral bone and cartilage. The present study evaluates the role of plasminogen activator inhibitor 1 (PAI-1) in bone-cartilage interaction and its direct effects on osteoarthritic cartilage.
Methods: Osteoblast culture supernatant from healthy (n=14) and OA (n=16) donors was tested on both healthy and OA cartilage and proteoglycan (PG) synthesis was studied. Expression levels of mediators were assessed in the osteoblast culture supernatants by Luminex analysis. Subsequently, OA cartilage (n=11 donors) was cultured in absence/presence of PAI-1 and PG synthesis changes were studied.
Results: PG synthesis of OA cartilage was increased (+34%, p=0.036) upon addition of healthy osteoblast supernatant. Importantly, a decrease was seen when OA osteoblast supernatant was added to healthy cartilage (-31% PG synthesis, p=0.001). PAI-1 was expressed at significant higher levels in healthy osteoblasts compared to OA osteoblasts (184ng/ml vs 91ng/ml, resp.p=0.015). Moreover, osteoblast PAI-1 levels were positively correlated with PG synthesis (r=0.595, p=0.042) influenced by the osteoblasts. Culturing OA cartilage in direct presence of PAI-1 (2000ng/ml) revealed 33% (p=0.026) increase of PG synthesis confirming the beneficial role of PAI-1 in the osteoblast cultures.
Conclusions: Healthy osteoblast derived mediators lead to PG synthesis increase in OA cartilage, while it has no effect on healthy cartilage. Moreover, OA osteoblast derived mediators lead to a decrease in PG synthesis in healthy cartilage, but not in OA cartilage. Higher PAI-1 levels in these osteoblasts cultures are clearly correlated with higher PG synthesis in cartilage, which hints at a role for PAI-1 in cartilage repair. Its direct effects on OA cartilage, increasing PG synthesis, further confirmed the relevance of PAI-1. This supports that targeting bone directly or involvement of bone might be feasible as treatment for OA.

508
INVOLVEMENT OF TGFß1 IN THE INITIAL PHASE OF TMJ AND KNEE OSTEOARTHRITIS

E.M. Long, R.E. Seegmiller, P. Reynolds. *Brigham Young Univ., Provo, UT, USA*

Purpose: The objective of this study was to elucidate OA progression in an animal model of Stickler syndrome by assessing the expression of an identified inflammatory marker associated with OA, viz., TGFß1. The study provides potential mechanistic insight into disease progression based on the temporal expression of TGFß1 in knee and temporomandibular joints (TMJ).
Methods: The study involved mice carrying the autosomal semidominant disproportionate micromelia (Dmm/+) mutation in the C-propeptide coding region of the Col2a1 gene. Specifically, six wild type control (+/+) and six heterozygous (Dmm/+) mice were evaluated for each joint. The mice were euthanized at three, six, and nine months of age, and their TMJs and knee joints were isolated, fixed, decalcified, embedded in paraffin, and sectioned at 6µm thickness. Three months of age coincides with the initial detection of histopathology in several murine models of OA. To determine OA status, selected tissues were stained with Safranin O to identify proteoglycans and counterstained with Fast Green. The extent of staining and onset of OA were quantified using Modified Mankin and OARSI scoring systems. Selected tissue sections of each genotype were also stained immunohistochemically for the presence of TGFß1, the inflammatory mediator that has been identified to play a role in OA progression.
Results: The results revealed Mankin and OARSI scores consistent with OA-like changes. These changes were detectable as early as three months in Dmm/+ mice when compared with normal joint biology observed in control animals. Compared to basal expression in control TMJs and knee joints, staining for TGFß1 demonstrated augmented expression in Dmm/+ mice as early as three months of age, with overexpression persisting in six-month-old mutant mice, but then disappearing at nine months of age. The present study demonstrated that TGFß1 was overexpressed in TMJ and knee articular cartilage of three- and six-month-old Dmm/+ mice when compared with age-matched controls.
Conclusions: Early TGFb1 expression levels suggested that this inflammatory mediator is involved in the earliest stages of TMJ OA. Further studies are underway that could shed light on TGFB1 and the use of other inflammatory markers such as HtrA1 and SMADs as possible targets for therapeutic intervention.

509
ACTIVATION OF THE RENIN-ANGIOTENSIN SYSTEM INTRODUCES OSTEOARTHRITIS

K. Yamagishi, I. Tsukamoto, M. Akagi. *Kinki Univ., Osakasayama City, Osaka, Japan*

Purpose: In 2013, we reported that the local renin-angiotensin system (RAS) can modulate the hypertrophic differentiation of chondrocytes.

The current study aimed to investigate whether hyperactivation of the RAS influences OA using forced-running mice models.
Methods: C57/BL6 mice and Tsukuba hypertensive mice (THM) were forced to run (25m/min, 30 min/day, 5days/week) (n=10). OA histopathology was analyzed using the OARSI score at 0, 2, 4, 6, and 8 weeks. Expression of type II collagen, type X collagen, MMP-13, ADAM-TS5 and some RAS components were also analyzed.
Results: The OARSI scores of the lateral femoral condyles were significantly higher in the THM than in the C57BL/6 mice at 4, 6 and 8 weeks. However, in medial femoral condyles, there were not significant differencesbetween C57/BL6 mice and THM. At 8 weeks, type II collagen was stained in a lower number of chondrocytes in the THM than C57/BL6 mice. The expression of type X collagen, MMP-13 and ADAM-TS5 was confirmed in the THM, but not in the C57/BL6 mice. In the THM, we compared the expression of angiotensin II type 1 receptor (AT1R) and AT2R at each week. At 0 weeks, we could not confirm the expression of AT1R and AT2R. However, we confirmed the expression of AT1R and AT2R at 2, 4, 6, 8 weeks.
Conclusions: We confirmed that the hyper activation of RAS induces OA changes in the lateral knee components of the mice under the load of forced running.

OA: Clinical Aspects

510
PRESENCE OF INTERLEUKIN-17 IN OSTEOARTHRITIS: DOES IT INDICATE A DIFFERENT OSTEOARTHRITIS PHENOTYPE

A. Lubbeke, S. Bas, G.J. Puskas, D. Suva, A. Finckh, C. Gabay, P. Hoffmeyer. *Geneva Univ. Hosp., Geneva, Switzerland*

Purpose: Interleukin-17 (IL-17) is an important factor in the pathogenesis of autoimmune diseases and allergy, and IL-17 antagonists are currently evaluated in randomized trials with encouraging results. In OA IL-17 contributes to cartilage breakdown and synovial infiltration by inducing the release of chemokines by chondrocytes and synovial fibroblasts independent of the IL-1 and TNF-α pathway. It also affects cartilage matrix turnover, induces angiogenesis in articular tissue, and amplifies joint inflammation. However, IL-17 is only infrequently detected in OA and clinical studies are sparse.
We aimed at evaluating the relation between absence or presence of IL-17 in synovial fluid (SF) of patients with endstage knee and hip OA and (1) other (adipo-)cytokine SF concentrations, and (2) clinical and radiographic disease parameters.
Methods: Cross-sectional study including patients prior to total hip (THA) and knee arthroplasty (TKA) operated upon for primary OA at a large tertiary hospital between January and December 2010. The morning of surgery concentrations of IL-17, IL-6, leptin, visfatin, adiponectin, resistin, MCP-1, MCP-3 and NGF were sampled from synovial fluid and assessed using ELISA kits. Baseline characteristics recorded preoperatively included age, sex, BMI, co-morbidities, pain and function (WOMAC), and radiographic analyses (OA features, K&L grade, minimal JSW).
Results: 152 patients were included, 68 prior to THA and 84 to TKA. Mean age was 73 (±9) years, 64% were women. In 14 patients (9.2%) IL-17 was present in the SF (median concentration 7.9 pg/ml, IQR 1.6; 20.6). These patients had significantly higher median SF concentrations of IL-6, leptin, resistin, MCP-3 and β-NGF, and a tendency to be female, younger, and obese class II, as compared to those without IL-17. Radiographic analyses revealed a significantly reduced minJSW together with a lower proportion of sclerosis and osteophytes in the presence of IL-17 in SF. No differences were found with respect to pain, function and comorbidities. There was a moderate correlation between Il-17 concentrations in SF and serum (r=0.482).
Conclusions: The presence of IL-17 in SF of patients with primary end stage OA was associated with high levels of several other proinflammatory adipokines, cytokines and chemokines, and with a different radiographic OA feature pattern. Moreover, patients tended to be younger, more often women and obese class II. Our results may indicate a different OA phenotype with a potential for a new treatment option.

511
ASSOCIATIONS BETWEEN KNEE PAIN SEVERITY AND PROGRESSION VERSUS MRI FEATURES: THE VANCOUVER LONGITUDINAL STUDY OF EARLY KNEE OA

E.C. Sayre †, A. Guermazi ‡, J.M. Esdaile §, J.A. Kopec §, H. Wong §, J. Singer §, A. Thorne §, S. Nicolaou §, J. Cibere §. † *Arthritis Res. Ctr. of Canada, Richmond, BC, Canada;* ‡ *Boston Univ. Med. Campus, Boston, MA, USA;* § *Univ. of British Columbia, Vancouver, BC, Canada*

Purpose: To determine the associations between knee pain severity and progression versus MRI features, including cartilage, osteophytes, bone marrow lesions (BML), subchondral sclerosis, meniscus, subchondral cysts and effusion, in a population-based cohort with knee pain.
Methods: Baseline, mean 3.3- and mean 7.5-year follow-up MRI assessments of the study (painful) knee were performed for 122 subjects with baseline knee pain, age 40-79 at baseline, sample-weighted for population (with knee pain) representativeness in Vancouver, BC (the Vancouver Longitudinal Study of Early Knee OA). MRIs were acquired on a 1.5T magnet at a single centre using a transmitter-receiver extremity knee coil, and 3 planes double-echo weighted sequences with and without fat suppression were obtained. MRIs were scored by a single experienced reader for cartilage (0=normal to 4=full thickness defect; 0/1 collapsed to 1=only signal change), BML (0=absent to 3=severe), subchondral sclerosis (0=absent to 3=severe) and subchondral cyst (0=absent to 3=severe) in 6 regions: lateral and medial femur, lateral and medial tibia, patella and trochlear groove. Meniscus (0=normal to 3=maceration/resection) was also scored in 6 regions: lateral anterior, lateral body, lateral posterior, medial anterior, medial body and medial posterior. Osteophytes (0=absent to 3=large) were scored in 8 regions: lateral and medial femur, lateral and medial tibia, and lateral, medial, superior and inferior patella. For each feature, region scores were added up and the sum divided by the number of regions. Effusion (0=absent to 3=severe) was scored for the overall knee and included as an indicator for >=2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain scale (normalized 0-100; higher numbers worse) was administered at each time point.
Cross-sectional models of pain were fit on 3 time points simultaneously (N=366), using generalized estimating equations (GEE) to account for correlated data. Longitudinal (change) models of delta pain, and indicators for 10+ points increase in pain, and 20+ points increase in pain were fit on both 2-cycle changes simultaneously (cycles 1-2 and 2-3; N=244), using GEE for binary or linear regression. Models for each feature were adjusted for age, sex and BMI (and follow-up time for longitudinal models).
Results: 55.7% of the weighted sample was female. At baseline, mean BMI was 26.1 and mean age was 55.5. Mean divided score sums at baseline were 1.74 for cartilage, 0.93 for osteophytes, 0.27 for BML, 0.08 for subchondral sclerosis, 0.48 for meniscus and 0.06 for subchondral cysts. Average normalized WOMAC pain at baseline was 19.1. 29.6% had baseline effusion >=2. Spearman rank correlations among the seven MRI features were all significantly >0, ranging from 0.21 (meniscus vs. subchondral cyst) to 0.68 (osteophyte vs. cartilage).
In cross-sectional regression models, osteophytes were significantly associated with pain (coefficient=7.17; 95% CI=3.19, 11.15), as was subchondral sclerosis (11.03; 0.68, 21.39). In longitudinal linear models of delta pain score, cartilage and osteophytes were significantly associated with pain change, respectively 4.31 (0.67, 7.95) and 4.51 (0.53, 8.49). In longitudinal binary models of delta pain score >=10, osteophytes (OR=3.20; 1.36, 7.55), subchondral sclerosis (OR=5.69; 1.06, 30.44), meniscus (OR=1.68; 1.08, 2.61) and effusion >=2 (OR=2.25; 1.07, 4.71) were significantly associated with pain increase. Finally, in binary models of delta pain score >=20, cartilage and osteophytes were significantly associated with pain increase, respectively OR=2.42 (1.24, 4.74) and 3.79 (1.41, 10.20). No associations were observed between pain severity or pain progression and BML or subchondral cysts, after adjusting for age, sex and BMI.
Conclusions: In this population-based cohort with 7-year follow-up we found a positive association between knee pain severity and both